



EXRESS MAIL CERTIFICATE

Date 4/22/02

Label No.

I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

B.W. LEE

Name (Print)

B.W. Lee

Signature

PLEASE CHARGE ANY DEFICIENCY UP TO \$300.00 OR
CREDIT ANY EXCESS IN THE FEES DUE WITH THIS
DOCUMENT TO OUR DEPOSIT ACCOUNT NO. 04-0100

Customer No.:



07278

PATENT TRADEMARK OFFICE

Docket No.: 9373/1H812-US3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Zhen -Gang WANG et al.

Serial No.: 10/016,668

Art Unit: 1642

Confirmation No.: 3843

Filed: 10/26/2001

Examiner: To be assigned

For: GENE RECOMBINATION AND HYBRID PROTEIN DEVELOPMENT

INFORMATION DISCLOSURE STATEMENT

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

In order to comply with the duty to disclose information under 37 C.F.R. § 1.56, Applicants submit herewith an Information Disclosure Statement Under 37 C.F.R. § 1.97 and § 1.98. In particular, Applicants submit herewith:

- (1) Form PTO-1449 listing references 1-112 for the Examiner's consideration; and

(2) Copies of references 91-100, 102 and 104-112 cited in the accompanying Form PTO-1449.

References 10-11, 14, 25, 36-37, 57-59 and 67 are general references of several hundred pages each. These references were previously made of record in U.S. Appln. Ser. No. 09/863,765 which is the parent of this application. To avoid overburdening the Examiner, copies of those references are not submitted herewith and were not submitted in the parent application. However, Applicants will provide copies of those references at the Examiner's request. Copies of references 1-9, 12-13, 15-24, 26-35, 38-56, 60-66 and 68-90 were also made of record in the parent application. Copies of the references may be found in the parent application.

To avoid over burdening the Examiner, copies of references 101 and 103 are not submitted herewith because they are general reference texts. However, Applicants will provide copies of those references at the Examiner's request.

This Information Disclosure Statement ("IDS") is being submitted in accordance with the requirement of 37 C.F.R. § 1.97(b). In particular, the IDS is submitted before the mailing of a first Office Action of the merits for this application. It is therefore believed that no fee is due for this submission. However, should the U.S. Patent and Trademark Office determine that any fee is required or that any refund is due for this submission, the Commissioner is hereby

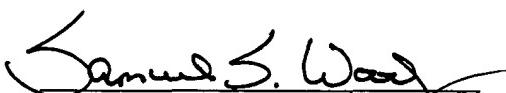
authorized and requested to charge any required fee(s) and/or credit any refund(s)
due to Deposit Account No. 04-0100.

In accordance with M.P.E.P. §§ 609 and 707.05(b), it is respectfully
requested that each document cited in the accompanying Form PTO-1449 be given
thorough consideration, and that all of the references be cited of record in the
prosecution history of the present application by initialing the Form PTO-1449 next
to each listed document. Such initialing is requested even if the Examiner does not
consider a cited document to be sufficiently pertinent to use in a rejection or
otherwise does not consider it to be prior art for any reason. This is requested so
that each document becomes listed on the face of the patent issuing from this
application. The citation of any document in this application is not to be construed
as an admission by Applicants or their representatives that such document is
necessarily relevant or prior art.

Early and favorable consideration of this Supplemental Information
Disclosure statement and the reference cited therein is earnestly solicited.

Respectfully submitted,

Dated: April 22, 2002



Samuel S. Woodley, Ph.D.
Registration No. 43,287
Agent for Applicant(s)

DARBY & DARBY
805 Third Avenue
New York, NY 10022
(212) 527-7700

Serial No. 10/016,668

Docket No. 9373/1H812-US3



U.S. DEPARTMENT OF COMMERCE PATENT & TRADEMARK OFFICE

SHEET 1 OF 10
(REV. 7-80)

LIST OF REFERENCES CITED BY APPLICANT

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812-US3 SERIAL NO: 10/016,668
APPLICANT: Zhen-Gang Wang et al. FILING DATE: 10-26-01
CONFIRMATION NO: 3843

U.S. PATENT DOCUMENTS

<u>*EXAMINER INITIALS</u>	<u>DOCUMENT NUMBER</u>	<u>DATE</u>	<u>NAME</u>	<u>CLASS</u>	<u>SUBCLASS</u>	<u>FILING DATE</u>
	1. 5,605,793	2/25/97	Stemmer	435	6	2/17/94
	2. 5,741,691	4/21/98	Arnold, <i>et al.</i>	435	197	1/23/96
	3. 5,811,238	9/22/98	Stemmer, <i>et al.</i>	435	6	11/30/95
	4. 5,830,721	11/3/98	Stemmer, <i>et al.</i>	435	172.1	3/4/96

FOREIGN PATENT DOCUMENTS

<u>*EXAMINER INITIALS</u>	<u>DOCUMENT NUMBER</u>	<u>DATE</u>	<u>COUNTRY</u>	<u>CLASS</u>	<u>SUBCLASS</u>	<u>TRANSLATION YES</u>	<u>NO</u>
	5. WO 95/22625	8/24/95	U.S.	C12Q	1/68		
	6. WO 97/20078	6/5/97	U.S.	C12Q	1/68		
				C12N	15/00		
				C07K	14/00		
	7.WO 98/42832	10/1/98	U.S.	C12N	15/09		
				C12P	19/34		

OTHER REFERENCES (INCLUDING AUTHOR, TITLE DATE, PERTINENT PAGES, ETC.)

*EXAMINER INITIALS

8. Affholter & Arnold, "Engineering a revolution," *Chemistry in Britain*, 1999, 35:48-51.
9. Almassy et al., "Structures of apo and complexed *Escherichia coli* glycinamide ribonucleotide transformylase", *Proc. Natl. Acad. Sci. U.S.A.*, 1992, 89:6114-6118.

LIST OF REFERENCES CITED BY APPLICANT

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812-US3 SERIAL NO: 10/016,668
APPLICANT: Zhen-Gang Wang et al. FILING DATE: 10-26-01
CONFIRMATION NO: 3843

*EXAMINER
INITIALS

10. Current Protocols in Molecular Biology, (Ausubel, F.M. et al. (Eds.), John Wiley & Sons, Inc. 1994). This is a general textbook of several hundred pages which we can provide upon request.
11. Animal Cell Culture, (R.I. Freshney, ed., Oxford University Press Inc. 1986). This is a general textbook of several hundred pages which we can provide upon request.
12. Arnold, "Advances in protein chemistry. Preface.", *Adv. Protein Chem.* 2000, **55**:ix-xi
13. Bairoch & Apweiler, " The SWISS-PROT protein sequence database and its supplement TrEMBL in 2000", *Nucl. Acids Res.*, 2000, **28**:45-48.
14. B.E. Perbal, A Practical Guide to Molecular Cloning (Wiley, John & Sons Inc., 1984). This is a general textbook of several hundred pages which we can provide upon request.
15. Benkovic et al., "A combinatorial approach to hybrid enzymes independent of DNA homology", *Nature Biotechnology*. 1999, **17**:1205-1209.
16. Berman et al., "The Protein Data Bank", *Nucl. Acids Res.*, 2000, **28**: 235-242.
17. Bogarad & Deem, "A hierarchical approach to protein molecular evolution", *Proc. Natl. Acad. Sci. U.S.A.*, 1999, **96**:2591-2595.
18. Brooks B.R. et al., "CHARMM: A Program for Macromolecular Energy, Minimization, and Dynamics Calculations", *J. Comp. Chem.*, 1983, **4**:187-217.
19. Colombo G & Mrez KM, "Stability and Activity of Mesophilic Subtilisin E and its Thermophilic Homolog: Insights from Molecular Dynamics Simulations", *J. Amer. Chem. Soc.*, 1999, **121**: 6895-6903.
20. Cornell et al., "A Second Generation Force Field for the Simulation of Proteins, Nucleic Acids, and Organic Molecules", *J. Amer. Chem. Soc.*, 1995, **117**: 5179-5197.
21. Crameri et al., "DNA shuffling of a family of genes from diverse species accelerates directed evolution", *Nature*, 1998, **391**:288-290.



FORM TT-1449

U.S. DEPARTMENT OF COMMERCE PATENT & TRADEMARK OFFICE

SHEET 3 OF 10
(REV. 7-80)**LIST OF REFERENCES CITED BY APPLICANT**

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812-US3 SERIAL NO: 10/016,668
APPLICANT: Zhen-Gang Wang et al. FILING DATE: 10-26-01
CONFIRMATION NO: 3843

*EXAMINER
INITIALS

22. Dahiyat et al., "Automated design of the surface positions of protein helices", *Protein Science*, 1997, 6:1333-1337.
23. Dahiyat & Mayo, "De Novo Protein Design: Fully Automated Sequence Selection", *Science*, 1997, 278: 82-87.
24. De Souza, et al., "Intron positions correlate with module boundaries in ancient proteins", *Proc. Natl. Acad. Sci. USA*, 1996, 93: 14632-14636.
25. DNA Cloning: A Practical Approach, Volumes I and II (B.D. Hames & D.M. Glover eds., Oxford University Press Inc., 1985). This is a general multiple volume textbook of several hundred pages which we can provide upon request.
26. Dube et al., "Selection of new biologically active molecules from random nucleotide sequences", *Gene*, 1993, 137:41-47.
27. Eisenberg, D & McLachlan AD, "Solvation Energy in Protein Folding and Binding", *Nature*, 1986, 319: 199-203.
28. Eisenberg D & Wesson L, "Atomic solvation parameters applied to molecular dynamics of proteins in solution", *Protein Science*, 1992, 1: 227-235.
29. Gilbert, et al., "Origin of Genes", *Proc. Natl. Acad. Sci. USA*, 1997, 94: 7698-7703.
30. Go, M., "Correlation of DNA exonic regions with protein structural units in haemoglobin", 1981, *Nature*, 291: 90-92.
31. Go, M., "Modular structural units, exons, and function in chicken lysozyme", *Proc. Natl. Acad. Sci. USA*, 1983, 80: 1964-1968.
32. Gordon and Mayo, "Radical Performance Enhancements for Combinatorial Optimization Algorithms based on the Dead-End Elimination Theorem", *J. Comp. Chem.*, 1998, 19(13): 1505-1514.
33. Hendsch ZS, Tidor B, "Do salt bridges stabilize proteins? A continuum electrostatic analysis", *Protein Science*, 1994, 3: 211-226.



FORM PTO-1449

U.S. DEPARTMENT OF COMMERCE PATENT & TRADEMARK OFFICE

SHEET 4 OF 10
(REV. 7-80)**LIST OF REFERENCES CITED BY APPLICANT**

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812-US3 SERIAL NO: 10/016,668
APPLICANT: Zhen-Gang Wang et al. FILING DATE: 10-26-01
CONFIRMATION NO: 3843

*EXAMINER
INITIALS

34. Hennecke, et al., "Random Circular Permutation of DsbA Reveals Segments that are Essential for Protein Folding and Stability", 1999, *J. Mol. Biol.*, **286**: 1197-1215.
35. Hogue *et al.*, "Structure Databases", *Methods Biochem. Anal.*, 1998, **39**: 46-73.
36. John H. Holland, Adaptation in Natural and Artificial Systems, (MIT Press, 1992) This is a general textbook of several hundred pages which we can provide upon request.
37. Immobilized Cells and Enzymes: A Practical Approach (IRL Press, 1986). This is a general textbook which we can provide upon request.
38. Jackson SE, et al., "Effect of Cavity-Creating Mutations in the Hydrophobic Core of Chymotrypsin Inhibitor 2", *Biochemistry*, 1993, **32**: 11259-11269.
39. Jermutus, et al., "Structure-based chimeric enzymes as an alternative to directed enzyme evolution: phytase as a test case", *J. Biotech.*, 2001, **85**: 15-24.
40. Joo *et al.*, "Laboratory evolution of peroxide-mediated cytochrome P450 hydroxylation", *Nature*, 1999, **399**: 670-673.
41. Kolkman & Stemmer, "Directed evolution of proteins by exon shuffling", *Nature Biotechnology*, 2001, **19**: 423-428.
42. Lazar GA, Desjarlais JR & Handel TM, "De Novo Design of the Hydrophobic core of ubiquitin", *Protein Science*, 1997, **6**:1167-1178.
43. Lee C & Levitt M, "Accurate prediction of the stability and activity effects of site-directed mutagenesis on a protein core", *Nature*, 1991, **352**: 448-451.
44. Lobkovsky *et al.*, "Evolution of an enzyme activity: Crystallographic structure at 2-Å resolution of cephalosporinase from *ampC* gene of *Enterobacter cloacae* P99 and comparison with a class A penicillinase", *Proc. Natl. Acad. Sci. U.S.A.*, 1993, **90**:11257-11261.



FORM PTO-1449

U.S. DEPARTMENT OF COMMERCE PATENT & TRADEMARK OFFICE

SHEET 5 OF 10
(REV. 7-80)LIST OF REFERENCES CITED BY APPLICANT

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812-US3 SERIAL NO: 10/016,668
APPLICANT: Zhen-Gang Wang et al. FILING DATE: 10-26-01
CONFIRMATION NO: 3843

*EXAMINER
INITIALS

45. MacKerell *et al.*, in *The Encyclopedia of Computational Chemistry*, Vol. 1:271-277, John Wiley & Sons, Chichester, 1998.
46. Malakaukas & Mayo, "Design, structure and stability of a hyperthermophilic protein variant", *Nature Structural Biology*, 1998, **5**:470-475.
47. Marchler-Bauer *et al.*, "MMDB: Entrez's 3D structure database", *Nucl. Acids Res.* 1999, **27**:240-243.
48. Mayo SL, Olafson BD & Goddard WAG, "DREIDING: A Generic Force Field for Molecular Simulations", *J. Phys. Chem.*, 1990, **94**: 8897-8909.
49. Mitra *et al.*, "A Novel Structural Basis for Membrane Association of Protein: Construction of a Chimeric Soluble Mutant of (S)-Mandelate Dehydrogenase from *Pseudomonas putida*", *Biochemistry*, 1993, **32**: 12959-12967.
50. Miyazaki *et al.*, "Directed Evolution Study of Temperature Adaptation in Psychrophilic Enzyme", *J. Mol. Biol.* 2000, **297**:1015-1026.
51. Miyazaki & Arnold, "Exploring Nonnatural Evolutionary Pathways by Saturation Mutagenesis: Rapid Improvement of Protein Function", *J. Molecular Evolution*, (1999) **49**:716-720.
52. Moore & Arnold, "Directed Evolution of a *para*-nitrobenzyl esterase for aqueous-organic solvents", *Nature Biotechnology*, 1996, **14**: 458-467.
53. Ness *et al.*, "Molecular Breeding - the natural approach to enzyme design", *Advances in Protein Chemistry*, 2000, **55**: 261-292.
54. Ness *et al.*, "DNA shuffling of subgenomic sequences of subtilisin", *Nature Biotechnology*, 1999, **17**:893-896.
55. Nielsen JE, Andersen KV, Honig B, Hooft RWW, Klebe G, Vriend G, & Wade RC, "Improving macromolecular electrostatics calculations", *Protein Engineering*, 1999, **12**: 657-662.
56. Nikolova *et al.*, "Semirational design of active tumor suppressor p53 DNA binding domain with enhanced stability", *Proc. Natl. Acad. Sci. U.S.A.*, 1998, **95**:14675-14680.



U.S. DEPARTMENT OF COMMERCE PATENT & TRADEMARK OFFICE

SHEET 6 OF 10
(REV. 7-80)

LIST OF REFERENCES CITED BY APPLICANT

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812-US3 SERIAL NO: 10/016,668
APPLICANT: Zhen-Gang Wang et al. FILING DATE: 10-26-01
CONFIRMATION NO: 3843

*EXAMINER
INITIALS

57. NMR of Macromolecules: A Practical Approach, (G.C.K. Roberts, Ed., Oxford University Press Inc., New York, 1993) This is a general text book of several hundred pages which we can provide upon request.
58. Nucleic Acid Hybridization, (B.D. Hames & S.J. Higgins, eds., Oxford University Press Inc., 1985). This is a general text book of several hundred pages which we can provide upon request.
59. Oligonucleotide Synthesis (M.J. Gait ed., Oxford University Press Inc., 1984). This is a general text book of several hundred pages which we can provide upon request.
60. Ostermeier et al., "Incremental truncation as a Strategy in the engineering of novel biocatalysts", *Bioorganic & Medicinal Chem.*, 1999, **7**: 2139-2144.
61. Pabo CO & Suchanek EG, "Computer-Aided Model-Building Strategies for Protein Design", *Biochemistry*, 1986, **25**: 5987-5991.
62. Pachenko, et al., "Foldons, protein structural modules, and exons", *Proc. Natl. Acad. Sci. USA*, 1996, **93**: 2008-2013.
63. Pikuleva, et al., "Studies of Distant Members of the P450 Superfamily (P450scc and P450c27) by Random Chimeragenesis", *Archives of Biochem. and Biophys.*, 1996, **334**:183-192.
64. Reeck et al., "'Homology in Proteins and Nucleic Acids: A Terminology Muddle and a Way out of it", *Cell* 1987, **50**:667.
65. Rossman, M. G. & Liljas, A., "Recognition of Structural Domains in Globular Proteins", *J. Molec. Biol.*, 1974, **85**: 177-181.
66. Saiki et al., "Primer-Directed Enzymatic Amplification of DNA with a Thermostable DNA Polymerase", *Science*, 1988, **239**:487-491.
67. Sambrook, Fitsch & Maniatis, Molecular Cloning: A Laboratory Manual, Second Edition (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York 1989). This is a three volume general practitioners book of several hundred pages which we can provide upon request.



FORM PTS 149 U.S. DEPARTMENT OF COMMERCE PATENT & TRADEMARK OFFICE

SHEET 7 OF 10
(REV. 7-80)

LIST OF REFERENCES CITED BY APPLICANT

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812-US3 SERIAL NO: 10/016,668
APPLICANT: Zhen-Gang Wang et al. FILING DATE: 10-26-01
CONFIRMATION NO: 3843

*EXAMINER
INITIALS

68. Schmidt-Dannert, et al., "Molecular breeding of carotenoid biosynthetic pathways", *Nature Biotechnology*, 2000, **18**:750-753.
69. Schneider JP, Lear JD, DeGrado WF, "A Designed Buried Salt Bridge in a Heterodimeric Coiled Coil," *J. Am. Chem. Soc.*, 1997, **119**:5742-5743.
70. Shimoji et al., "Design of a Novel P450: A Functional Bacterial - Human Cytochrome P450 Chimera", *Biochemistry*, 1998, **37**: 8848-8852.
71. Sidelar CV, Hendsch ZS, Tidor B, "Effects of salt bridges on protein structure and design", *Protein Science*, 1998, **7**: 1898-1914.
72. Sieber et al., "Libraries of hybrid proteins from distantly related sequences", *Nature Biotechnology*, 2000, **19**, 456-460.
73. Skandalis et al., "Creating novel enzymes by applied molecular evolution", *Chem. Biol.*, 1997, **4**:889-898.
74. Stemmer, "DNA shuffling by random fragmentation and reassembly: *In vitro* recombination for molecular evolution", *Proc. Natl. Acad. Sci.*, 1994, **91** :10747-10751.
75. Stemmer, "Rapid evolution of a protein *in vitro* by DNA shuffling", *Nature*, 1994, **370**:389-391.
76. Stikoff D, Lockhart DJ, Sharp KA & Honig B, "Calculation of electrostatic effects at the amino-terminus of an alpha-helix", *Biophys. J.*, 1994, **67**: 2251-2260.
77. Street AG & Mayo SL, "Pairwise calculation of protein solvent-accessible surface areas", 1998, **3**: 253-258.
78. Street & Mayo, "Computational protein design", *Structure*, 1999, **7**: R105-R109.
79. Tatusova, T. A. & Madden T. L., "BLAST 2 Sequences, a new tool for comparing protein and nucleotide sequences", *FEMS Microbiol Lett.*, 1999, **174**:247-250.



FORM PTO-1449

U.S. DEPARTMENT OF COMMERCE PATENT & TRADEMARK OFFICE

SHEET 8 OF 10
(REV. 7-80)**LIST OF REFERENCES CITED BY APPLICANT**

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812-US3 SERIAL NO: 10/016,668
APPLICANT: Zhen-Gang Wang et al. FILING DATE: 10-26-01
CONFIRMATION NO: 3843

*EXAMINER
INITIALS

80. Tsai, C-J., et al., "Anatomy of protein structure: Visualizing how a one-dimensional protein folds into a three-dimensional shape", *Proc. Nat. Acad. Sci., USA*, 2000, **97**:12038-12043.
81. Volkov et al., "Methods for *in Vitro* DNA Recombination and Random Chimeragenesis", *Methods Enzymol.*, 2000, **328**: 447-456.
82. Volkov et al., "Recombination and chimeragenesis by *in vitro* heteroduplex formation and *in vivo* repair", *Nucl. Acids Res.*, 1999, **27**:e18, i-vi.
83. Wang et al., "MMDB: 3D structure data in Entrez", *Nucl. Acids Res.*, 2000, **28**:243-245.
84. Weiner et al., "A New Force Field for Molecular Mechanical Simulation of Nucleic Acids and Proteins" *J. Amer. Chem. Soc.*, 1984, **106**:765-784.
85. Weiner et al., "An All Atom Force Field for Simulations of Proteins and Nucleic Acids", *J. Comp. Chem.*, 1986, **7**:230-252.
86. Woods et al., "Molecular Mechanical and Molecular Dynamical Simulations of Glycoproteins and Oligosaccharides. 1. GLYCAM_93 Parameter Development", *J. Phys. Chem.*, 1995, **99**:3832-3846.
87. Zhao & Arnold, "Combinatorial protein design: strategies for screening protein libraries", *Curr. Op. St. Biol.*, 1997, **7**: 480-485.
88. Zhao & Arnold, "Directed evolution converts subtilisin E into a functional equivalent of thermitase", *Protein Engineering*, 1999, **12**:47-53.
89. Zhao & Arnold, "Optimization of DNA shuffling for high fidelity recombination", *Nucleic Acids Res.*, 1997, **25**:1307-1308.
90. Zhao et al., "Molecular evolution by staggered extension process (StEP) in vitro recombination," *Nat. Biotechnology*, 1998, **16**(3):258-61.
91. Jelsch, C., Mourey, L., Masson, J. M., & Samama, J. P., "Crystal Structure of *Escherichia coli* TEM1 Proteins., 1993, **16**: 364-383

APR 22 2002

LIST OF REFERENCES CITED BY APPLICANT

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812-US3 SERIAL NO: 10/016,668
APPLICANT: Zhen-Gang Wang et al. FILING DATE: 10-26-01
CONFIRMATION NO: 3843

*EXAMINER
INITIALS

92. Sanschagrin F, Theriault E, Sabbagh Y, Voyer N, Levesque RC, "Combinatorial biochemistry and shuffling of TEM, SHV and *Streptomyces albus* omega loops in PSE-4 class A β -lactamase", *J. Antimicro. Chemo.*, 2000, **45**: 517-519.
93. Crippen, G. M., "The Tree Structural Organization of Proteins", *J. Mol. Biol.*, 1978, **126**: 315-332
94. Rose, G. D., "Hierarchic Organization of Domains in Globular Proteins", *J. Mol. Biol.*, 1979, **134**: 447-470
95. Zehfus, M. H. & Rose, G. D., "Compact Units in Proteins", *Biochemistry*, 1986, **25**: 5759-5765
96. Holm, L. & Sander, C., "Parser for Protein Folding Units", *Proteins*, 1994, **19**: 256-268
97. Panchenko, A. R., Luthey-Schulten, Z. & Wolynes, P. G., "Foldons, protein structural modules, and exons", *Proc. Natl. Acad. Sci. USA*, 1996, **93**: 2008-2013
98. Ranganathan, A., et al., "Knowledge-based design of bimodular and trimodular polyketide synthases based on domain and module swaps: a route to simple stain analogues", *Chem Biol.*, 1999, **6**: 731-741
99. Riechmann, L. and Winter, G., "Novel folded protein domains generated by combinatorial shuffling of polypeptide segments", *Proc. Natl. Acad. Sci. USA*, 2000, **97**: 10068-10073
100. Lutz, S. & Benkovic, S. J., "Homology-independent protein engineering", *Curr. Opin. Biotech.*, 2000, **11**: 319-324
101. Holland, J. (1975) *Adaptation in Natural and Artificial Systems* (The University of Michigan Press, Ann Arbor, MI). This is a general textbook that we can provide upon request.
102. Forrest, S. & Mitchell, M., "Relative Building-Block Fitness and the Building-Block Hypothesis", in *Foundations of Genetic Algorithms* 2, ed. Whitley, L. D. (Morgan Kaufmann, San Mateo), 1993, pp. 109-126
103. Mitchell, M. (1996) *An Introduction to Genetic Algorithms* (The MIT Press). This is a general textbook that we can provide upon request.

LIST OF REFERENCES CITED BY APPLICANT

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812-US3 SERIAL NO: 10/016,668
APPLICANT: Zhen-Gang Wang et al. FILING DATE: 10-26-01
CONFIRMATION NO: 3843

*EXAMINER
INITIALS

104. Ostermeier, M., Shim, J. H. & Benkovic, S. J., "A combinatorial approach to hybrid enzymes independent of DNA homology", *Nature Biotechnology*, 1999, **17**: 1205-1209
105. Brock, B. J., & Waterman, M. R., "The Use of Random Chimeragenesis to Study Structure/Function Properties of Rat and Human P450c17", *Arch. Biochem. Biophys.*, 2000, **373**: 401-408
106. Lutz, S., Ostermeier, M., & Benkovic, S. J., "Rapid generation of incremental truncation libraries for protein engineering using α -phosphothioate nucleotides", *Nucl. Acid. Res.*, 2001, **29**:4 e16
107. Betzel, C., Klupsch, S., Papendorf, G., Hastrup, S., Branner, S., & Wilson, K. S., "Crystal Structure of the Alkaline Proteinase Savinase™ from *Bacillus lentinus* at 1·4 Å Resolution", *J. Mol. Biol.*, 1992, **223**: 427-445
108. Williams, P. A., Cosme, J., Sridhar, V., Johnson, E. F., and Mcree, D. E., "Mammalian Microsomal Cytochrome P450 Monooxygenase: Structural Adaptations for Membrane Binding and Functional Diversity", *Mol. Cell.*, 2000, **5**: 121-131
109. Horton, R. M., "PCR-Mediated Recombination and Mutagenesis" *Mol. Biotech.*, 1995, **3**: 93-99
110. Lim, D., Sanschagrin, F., Passmore, L., De Castro, L., Levesque, R. L., & Strynadna N. C. J., "Insights into the Molecular Basis for the Carbenicillinase Activity of PSE-4 β -Lactamase from Crystallographic and Kinetic Studies", *Biochemistry*, 2001, **40**: 395-402
111. Voigt, C. A., Mayo, S. L., Arnold, F. H., & Wang, Z-G., "Computational method to reduce the search space for directed protein evolution", *Proc. Natl. Acad. Sci. USA*, 2001, **98**: 3778-3783
112. Voigt, C. A., Kauffman, S., & Wang, Z-G., "Rational Evolutionary Design: the Theory of *In Vitro* Protein Evolution", *Advances in Protein Chemistry*, 2001, **55**: 79-160